

Effect of Acrycoat S100 Concentrations on the Entrapment Efficiency of Domperidone in Microsphere

Rise Desnita, Uli Maulana, Pratiwi Apridamayanti

Department of Pharmacy, Faculty of Medicine, University of Tanjungpura, Jl. Profesor Dokter H. Hadari Nawawi, Bansir Laut, Pontianak Tenggara, Kota Pontianak, Kalimantan Barat, Indonesia

Abstract

Introduction: Domperidone is an antiemetic that is greatly absorbed in the upper part of the gastrointestinal tract in acidic pH and significantly reduced in alkaline pH. Bioavailability of domperidone is 13–17%. One of an effort in increasing the bioavailability of domperidone is to make a microsphere system that was resistance in the upper part of the gastrointestinal tract. Acrycoat S100 is a polymer that can be used for making a microsphere system and for extended release of the drug. **Materials and Methods:** This study aims to determine the effect of Acrycoat S100 concentration on entrapment efficiency of domperidone in microsphere which is formulated in four formulas that are F1 50 mg, F2 100 mg, F3 150 mg, and F4 200 mg, containing domperidone and Acrycoat S100 as the materials. The method of making microsphere was solvent evaporation. The entrapment efficiency of domperidone in microsphere was determined using ultraviolet spectroscopic method, and entrapment efficiency data were statistically analyzed using SPSS One-way analysis of variance (ANOVA) program. The characterization of domperidone microspheres was organoleptic, particle size measurement and morphology observation using Scanning Electron Microscope (SEM). **Results:** The result of the determination of entrapment efficiency showed that increasing the concentration of Acrycoat S100 is directly proportional to increasing the entrapment efficiency of domperidone in microsphere and F3 formula has an optimum entrapment efficiency by $78.723\% \pm 4.259$ from the statistical analysis with SPSS One-way ANOVA. Domperidone microsphere was a physically white powder with a distinctive odor. The particle size of microsphere domperidone was 31.88–319.87 μm . The morphology of domperidone microsphere observed with SEM was spheric with rough surface, and the size was 172.9 μm . **Discussion:** Optimum entrapment efficiency of domperidone in microsphere that was formulated with Acrycoat S100 was $78.723\% \pm 4.259$ and increasing with the increasing of the Acrycoat S100 as its polymer with solvent evaporation method. It might be more with high concentrations of Acrycoat S100. **Conclusion:** The concentration of Acrycoat S100 was a crucial parameter in entrapment efficiency of domperidone in the microsphere.

Key words: Acrycoat S100, domperidone, entrapment efficiency, microsphere

INTRODUCTION

The microsphere is a drug delivery system for extended-release by controlling drug release (controlled release). The microsphere is a matrix system containing drugs and suitable for oral use. The microsphere is spherically solid with a size of 1–1000 μm , in the form of powders containing protein or synthetic polymers. The microsphere is a homogeneous structure so that the drug can be dispersed out of the matrix.^[1] The drug will release from the microsphere system through the pores or gaps present in the matrix by diffusion.^[2] Microsphere can generally improve the quality of treatment of patients by extending drug release time so as to reduce the frequency

of drug use.^[3] The microsphere is chosen as a delivery system that can solve a variety of problems, for example, for drugs with short half-life, unstable drugs, low bioavailability, and high frequency of drug use.^[4]

Domperidone [Figure 1] is an antiemetic based on dopamine receptor blockage in Chemo Trigger Zone. Half-time of

Address for correspondence:

Uli Maulana, Jl Atot Ahmad Komplek Sejahtera Asri Blok H No. 7 Perum 2, Jeruju, Pontianak Barat, 78113, Kalimantan Barat, Indonesia. Phone: +62-81-256141386. E-mail: ulimaulana21@gmail.com

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domperidone is approximately 7 h.^[5,6] The bioavailability of oral of domperidone is low about 13–17%.^[7] The solubility of domperidone is low in alkaline pH so it can precipitate in its formulation if it is in the gut. As a result, domperidone cannot be absorbed by the body. However, domperidone is well absorbed in the stomach due to its good solubility in acidic pH,^[8-10] so it is suitable to make microsphere domperidone with the aim of prolonging the domperidone dwell time in the stomach so as to increase its bioavailability.^[11,12]

Acrycoat S100 or methacrylic acid copolymers are polymers that can be used to form microspheres. Acrycoat S100 is a white powder with a slightly acidic smell. Acrycoat S100 is recommended for extended drug release systems, and it is resistant to gastric acid but dissolves at pH 7 and forms salt at a higher pH. The density of Acrycoat S100 (0.24 g/mL) is lower than the density of the gastric fluid (1.004 g/mL), so Acrycoat S100 provide a floating system of microsphere. Acrycoat S100 is a large molecular polymer that is not toxic to the body and is used as a drug release controller.^[11,13]

The entrapment efficiency of the drug is directly proportional to the polymer concentration. Increased polymer concentrations may increase drug entrapment efficiency.^[14] This study aims to determine the effect of Acrycoat S100 concentration on domperidone entrapment efficiency in the microsphere. The determination of domperidone entrapment efficiency is done by ultraviolet (UV) spectroscopic method.

MATERIALS AND METHODS

Materials

Domperidone (Dexa Medica, Indonesia) as active pharmaceutical ingredient, Acrycoat S100 (Corel Pharma Chem, Ahmedabad) as a polymer to form microsphere, ethanol, and dichloromethane (DCM) (Brataco, Indonesia) as organic solvent to dissolve domperidone and Acrycoat S100, polyvinyl alcohol (PVA) as stabilizing agent, distilled water (Widatra Bhakti, Indonesia) as a medium for emulsification process and methanol (Merck, German) as solvent to determine the entrapment efficiency of domperidone in microsphere. All materials used in this research were purchased and were analytical grade.

Preparation of domperidone microsphere

Domperidone microspheres were made into four formulas with variation concentration of Acrycoat S100 [Table 1]. The domperidone solution was prepared by dissolving domperidone and Acrycoat S100 in an organic solvent mixture of ethanol: DCM in a 1:1 ratio of 20 mL (10 mL ethanol: 10 mL DCM). The PVA, 0.05% solution, was prepared by dissolve 50 mg PVA in 100 mL hot distilled water. The domperidone solution and PVA solution were mixed and then stirred at a rate of 500 rpm for 120 min at room temperature.

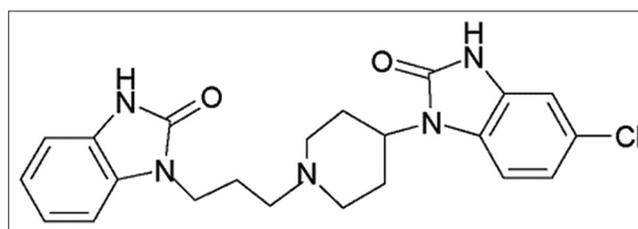


Figure 1: Structure of domperidone

Table 1: Formula of domperidone microsphere

Material	Formula			
	F1	F2	F3	F4
Domperidone (mg)	50	50	50	50
Acrycoat S100 (mg)	50	100	150	200
Ethanol: DCM (1:1) (ml)	20	20	20	20
PVA (mg)	50	50	50	50
Distilled water (mL)	100	100	100	100

PVA: Polyvinyl Alcohol, DCM: Dichloromethane

The domperidone microsphere was formed by diffusion and solvent evaporation. Furthermore, microsphere domperidone that was dispersed in a water medium is filtered, washed with water several times and dried in a desiccator for 24 h.

Curve calibration of domperidone

Domperidone stock solution (100 ppm) was prepared by dissolving 10 mg domperidone which was accurately weighed in methanol in a 100 ml measuring flask. The mixture was stirred to homogeneous.^[12,15] The series concentrations were made from stock solutions including 8, 12, 16, 20, and 24 ppm. The absorbance of each series was measured by a UV spectrophotometer (Shimadzu 2450) at the maximum wavelength. The maximum wavelength of domperidone was found at 286.5 nm.

Determination of domperidone entrapment efficiency in microspheres

Domperidone microspheres were weighed 5 mg and dissolved in 10 ml of methanol. Then, the solution containing domperidone was measured using a UV spectrophotometer at the maximum wavelength. The concentration of percent efficiency rate was calculated using the formula: ^[16]

$$\% \text{ EE} = (\text{Weight of drug in microsphere} / \text{Weight of theoretical drug}) \times 100$$

Characterization of domperidone microspheres

Organoleptic observation

Organoleptic observations include colors, odors, and shapes of domperidone microspheres performed using the five senses.

Particle size measurement

Microsphere particle size measurements were performed using Axio Cam optical microscope with $\times 10$ and $\times 40$ magnification.

Morphology observation using scanning electron microscope (SEM)

The morphology of domperidone microsphere was observed with SEM (JEOL JSM 6510 LA). Scanning was done by placing a few of microspheres on the glass stub section then placed in scanning electron chamber.^[17] Scanning was done at $\times 400$ magnification.

Data analysis

Data of the entrapment efficiency domperidone in microsphere each formulas were analysis with SPSS One-way analysis of variance (ANOVA) program.

RESULTS

Domperidone microspheres

In this research, domperidone microspheres were made by a solvent evaporation method. The reason for using solvent evaporation method on the manufacture of domperidone microsphere was that easy to do and is compatible with the microsphere material used. The principle of this method was the formation of solid droplets on the medium with the help of stabilizing agents.

Consideration of the selection of Acrycoat S100 as the microsphere polymer in this study was Acrycoat S100 has a good ability to absorb drugs in a microsphere system by a solvent evaporation method and can control drug release with lower density than the gastric fluid density.^[13] Acrycoat S100 is a polymer that is resistant to acidic pH but is soluble in alkaline pH, so it is expected to last long in the stomach with floating microsphere system and can increase the solubility of domperidone bioavailability. Domperidone will release from the microsphere system by diffusion when it comes directly to the gastric fluid. Hence, the domperidone release system out of the matrix becomes a controlled release. The empty microsphere will be transported to the intestine and dissolve in the intestinal pH so that it can be removed from the body.

The domperidone microsphere that form of solid particles dispersed in an aqueous medium in the water medium process will be filtered. Microsphere domperidone in the form of a powder suspended in filter paper and then dried in a desiccator for 24 h then weighed. The dried domperidone microsphere then separated from the filter paper by grinding. The domperidone microsphere obtained in a physical formulation was white powder with odorless odor. The physical form of the domperidone microsphere can be seen in Figure 2.

Curve calibration of domperidone

Determination of the maximum wavelength of domperidone was carried out in the UV region with a search range of 250–300 nm. The maximum wavelength of domperidone in methanol according to King *et al.* in 2008 was 284 nm^[18] and 287 nm according to Mjekodunmi *et al.* in 2017.^[12] The maximum wavelength of domperidone in methanol with a concentration of 8 ppm was 286.5 nm. The calibration curve of domperidone in methanol was made with a series of concentrations of which are 8, 12, 16, 20, and 24 ppm. The regression obtained was $y = 0.030x - 0.006$. Data calibration curve can be seen in Figure 3.

The entrapment efficiency of domperidone in the microsphere

Percentage entrapment efficiency of domperidone in microsphere was determined using UV-visible spectrophotometric method. The domperidone microsphere weighed 5 mg and dissolved in 10 ml of methanol. Domperidone absorbance was measured by UV-visible spectrophotometer at the maximum wavelength. The data of percentage entrapment efficiency of the formula of domperidone microspheres F1, F2, F3, and F4 can be seen in Table 2 and Figure 4. Based on the data, it was known that the concentration of Acrycoat S100 affects the percentage efficiency of domperidone entrapment in the microsphere. Increasing the concentration of Acrycoat S100 is directly proportional to increasing the percentage entrapment efficiency of domperidone in the microsphere.

Characterization of domperidone microsphere

Organoleptic observation

Organoleptic observations performed on the microsphere domperidone include colors, odors, and shapes performed using the five senses. The result of a physically formed microsphere domperidone was a white powder with a

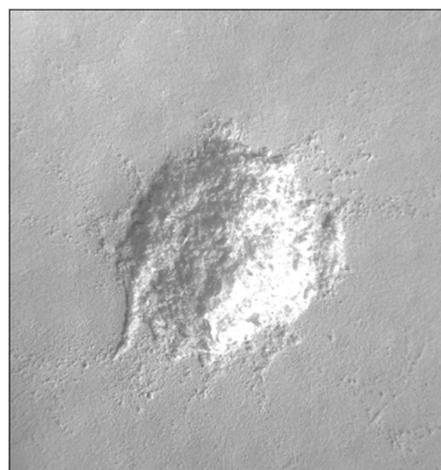
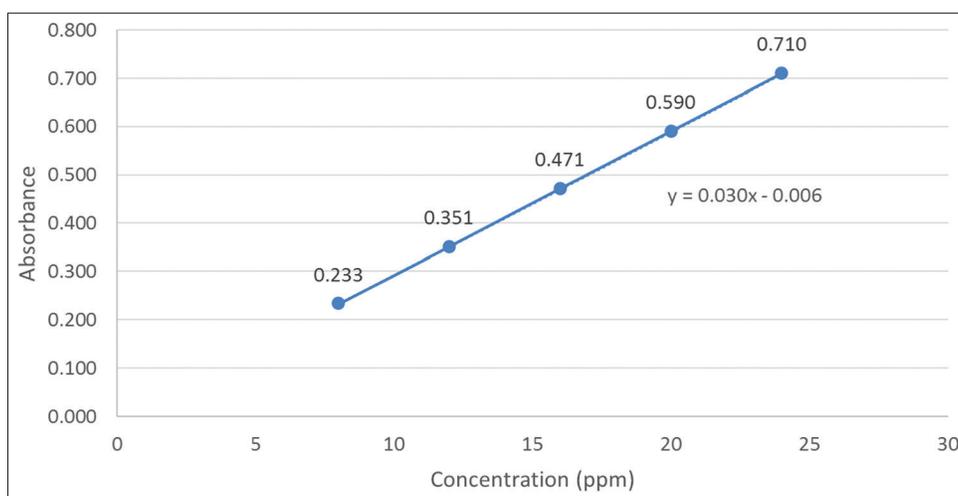
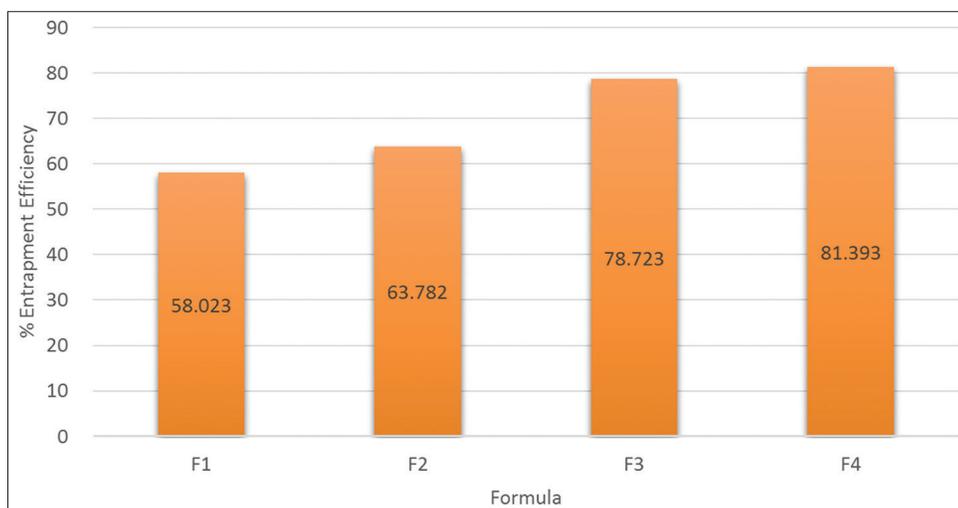


Figure 2: Domperidone microspheres

Table 2: Percentage entrapment efficiency of domperidone in the microsphere

Formula	Absorbance	Weight of domperidone microspheres (mg)	Entrapment efficiency (% EE)	Average entrapment efficiency (% EE)±SD
F1	0.503	94.3	64.003	58.023±6.872
	0.534	82.7	59.548	
	0.434	86.1	50.517	
F2	0.656	147	64.782	63.782±7.833
	0.272	149.7	55.497	
	0.368	142.5	71.068	
F3	0.632	192.3	81.797	78.723±4.259
	0.578	189.7	73.862	
	0.599	199.6	80.511	
F4	0.527	248.6	88.342	81.393±6.021
	0.477	241.4	77.737	
	0.465	248.7	78.098	

**Figure 3:** Curve calibration of domperidone. ppm-part per million**Figure 4:** Entrapment efficiency of domperidone in the microsphere [Table 1]. F1 contains 50 mg Acrycoat S100 and 50 mg domperidone, F2 contains 100 mg Acrycoat S100 and 50 mg domperidone, F3 contains 150 mg Acrycoat S100 and 50 mg domperidone, F4 contains 200 mg Acrycoat S100 and 50 mg domperidone

distinctive odor (odorless). There was no large difference in color, odor, and shape in the four formulas of the domperidone microspheres.

Particle size measurement

Domperidone microsphere particle size measurements were performed using an optical microscope. The size of the microsphere domperidone particle obtained was 31.88–319.87 μm .

Morphology observation using SEM

SEM analysis was performed to determine the morphology of domperidone microspheres. The magnification used in the observation was $\times 400$. The data of SEM observation can be seen in Figure 5. Based on the picture, it was found that

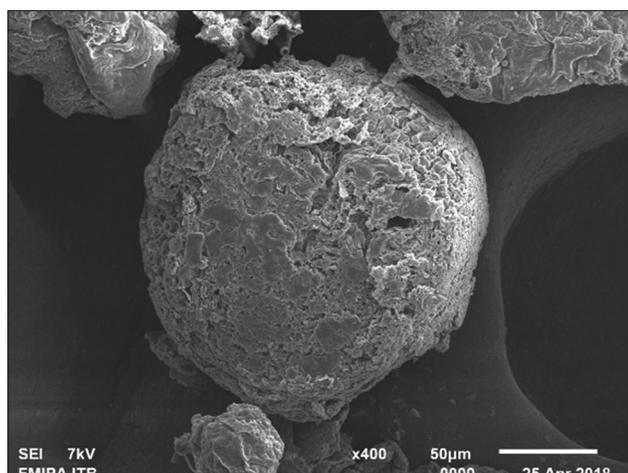


Figure 5: Morphology observation of domperidone microspheres using scanning electron analysis with $\times 400$ magnification

the shape of the domperidone microspheres was spherical with a rough surface and the size was 172.9 μm . According to research by Panwar *et al.* in 2015, that the microsphere formulated with Acrycoat has a spherical and rough surface.^[19]

Data analysis

The result of percentage entrapment efficiency was analyzed by SPSS statistical analysis program. The purpose of the analysis was to determine the formula of the microsphere which results in the optimum entrapment efficiency. This analysis was performed using One-way ANOVA analysis. The result of the statistical analysis of percentage entrapment efficiency can be seen in Figure 6. Based on the analysis, it can be concluded that there was a significant difference in the value of the entrapment efficiency (sig. = 0.005) in all four formulas with $P < 0.05$. Formula F1 and F2 have no significantly different but have a significant difference with the formula F3 and F4. Formula F3 does not have a significant difference in the value of a significant entrapment efficiency with F4. Thus, the concentration of Acrycoat S100 selected as the concentration which can provide optimum entrapment efficiency was the formula F3 containing 50 mg domperidone and 150 mg Acrycoat S100 with the value of the entrapment efficiency of $78.723\% \pm 4.259$.

DISCUSSION

Arabinda Patnaik observed that microsphere cinnarizine that was made by polymer Acrycoat S100 with solvent evaporation method showed the best performance of releasing, buoyancy and high entrapment efficiency compared with ethyl cellulose and Eudragit Rs. 100. The concentration of

Multiple Comparisons						
Dependent Variable: entrapment_efficiency						
LSD						
(I) formula	(J) formula	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
F1	F2	-5.759667	5.211692	.301	-17.77785	6.25852
	F3	-20.700667*	5.211692	.004	-32.71885	-8.68248
	F4	-23.369667*	5.211692	.002	-35.38785	-11.35148
F2	F1	5.759667	5.211692	.301	-6.25852	17.77785
	F3	-14.941000*	5.211692	.021	-26.95918	-2.92282
	F4	-17.610000*	5.211692	.010	-29.62818	-5.59182
F3	F1	20.700667*	5.211692	.004	8.68248	32.71885
	F2	14.941000*	5.211692	.021	2.92282	26.95918
	F4	-2.669000	5.211692	.622	-14.68718	9.34918
F4	F1	23.369667*	5.211692	.002	11.35148	35.38785
	F2	17.610000*	5.211692	.010	5.59182	29.62818
	F3	2.669000	5.211692	.622	-9.34918	14.68718

*. The mean difference is significant at the 0.05 level.

Figure 6: One-way analysis of variance data analysis. *There is significant difference

Acrycoat S100 that was used in that observation was 50 mg, 100 mg, 150 mg, and 200 mg. High entrapment efficiency of cinnarizine microsphere showed with the use of 100 mg of Acrycoat S100 that was 91%, and content of releasing was 98.14% during 12 h.^[13]

Microsphere domperidone that was made with the same method showed that 150 mg of Acrycoat S100 had a optimum entrapment efficiency that was 78.723% \pm 4.259. It was different with the observation done by Patnaik. It might due to the different characteristic of cinnarizine and domperidone. Microsphere needs more concentration of Acrycoat S100 to entrapped domperidone in it.

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